Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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CONSENSUS REPORT

The convergence of advances in medical science, human biology, data science, and technology has enabled the generation of new insights into the phenotype known as "diabetes." Increased knowledge of this condition has emerged from populations around the world, illuminating the differences in how diabetes presents, its variable prevalence, and how best practice in treatment varies between populations. In parallel, focus has been placed on the development of tools for the application of precision medicine to numerous conditions. This Consensus Report presents the American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative in partnership with the European Association for the Study of Diabetes (EASD), including its mission, the current state of the field, and prospects for the future. Expert opinions are presented on areas of precision diagnostics and precision therapeutics (including prevention and treatment), and key barriers to and opportunities for implementation of precision diabetes medicine, with better care and outcomes around the globe, are highlighted. Cases where precision diagnosis is already feasible and effective (i.e., monogenic forms of diabetes) are presented, while the major hurdles to the global implementation of precision diagnosis of complex forms of diabetes are discussed. The situation is similar for precision therapeutics, in which the appropriate therapy will often change over time owing to the manner in which diabetes evolves within individual patients. This Consensus Report describes a foundation for precision diabetes medicine, while highlighting what remains to be done to realize its potential. This, combined with a subsequent, detailed evidence-based review (due 2022), will provide a roadmap for precision medicine in diabetes that helps improve the quality of life for all those with diabetes.

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RATIONALE FOR PRECISION MEDICINE IN DIABETES

The practice of medicine centers on the individual. From the beginning, the physician has examined the patient suffering from illness, ascertained his/her signs and symptoms, related them to the medical knowledge available at the time, recognized patterns that fit a certain category and, based on the practical wisdom accumulated via empirical trial and error, applied a given remedy that is best suited to the situation at hand. Thus, the concept of *precision medicine*, often defined as

providing the right therapy for the right patient at the right time, is not novel. What has changed radically is our ability to characterize and understand human biological variation through *1*) assessment of the genetic and metabolic state, *2*) leveraging data to inform disease categories, and *3*) science-guided preventive and treatment decisions tailored to specific pathological conditions. Coupling these with detailed information about lifestyle and environment, available through digital devices and technologies that collect those measures, as well as data abstracted from electronic medical records, present unparalleled opportunities to optimize diabetes medicine.

Diabetes mellitus is diagnosed by the presence of hyperglycemia that is higher than a threshold blood glucose concentration which predisposes to microvascular end-organ complications. However, hyperglycemia is the end product of numerous pathophysiological processes that often emerge over many years and converge on the inability of the pancreatic β-cells to secrete enough insulin to meet the demands of target tissues. In clinical practice, absolute insulin deficiency can be detected from the autoimmune destruction of β-cells in type 1 diabetes (T1D), which represents ~10% of all diabetes cases. Making the diagnosis of T1D is critical for survival, given the therapeutic requirement of exogenous administration of insulin. However, less commonly, hyperglycemia might derive from an inherited or de novo loss of function in a single gene (e.g., monogenic diabetes, comprising 2–3% of all diabetes diagnosed in children or young adults). Diabetes can also appear after pancreatitis or organ transplantation, during pregnancy, or as a result of cystic fibrosis. Most individuals with diabetes, however, are likely to be diagnosed with type 2 diabetes (T2D), which includes defects in one or (more often) multiple physiological pathways (e.g., β-cell insufficiency, fat accumulation or miscompartmentalization, inflammation, incretin resistance, dysfunctional insulin signaling).

Our modern capacity to comprehensively interrogate diverse axes of biology has facilitated the approach of studying an individual to infer general principles, from which a discrete treatment plan is selected. These axes include developmental/metabolic context, genomic variation, chromatin signals that mark genes as active or repressed in tissues, expressed transcripts, biomarkers of disease, and increased knowledge of lifestyle/environmental risk factors. Parallel advances in computational power and analytical methods required to appropriately interrogate "big data" are driving insights that may radically transform the practice of medicine. Yet, at this time, the individual physician often lacks the time and training needed to incorporate these insights into medical decision making. Thus, the translation of the rapidly accumulating new knowledge into practice requires careful evaluation and translational strategies involving specialist training, education, and policy considerations.

The failure to adequately understand the diverse molecular and environmental processes that underlie diabetes and our inability to identify the pathophysiological mechanisms that trigger diabetes in individual patients limit our ability to prevent and treat the disease. Public health strategies have struggled to slow the epidemic, even in countries with the greatest financial and scientific resources. Pharmacological therapies, comprising 12 different drug classes currently approved by the U.S. Food and Drug Administration (FDA), may, at best, control blood glucose and modify disease course but do not provide a cure or result in the remission of disease. Moreover, these agents are sometimes prescribed based on nonmedical considerations (cost, side effects, patient preference, or comorbidities), which may overlook the biological mechanism. Thus, more people are developing diabetes worldwide and have disease progressing to complications, incurring a significant health care burden and cost.

There are, however, several reasons for hope. First, diabetes caused by single gene defects can be characterized and targeted therapies are particularly effective (1,2). Second, islet autoantibody biomarkers and genomic risk have clarified autoimmune diabetes from other forms of the disease (3,4), thereby facilitating immune intervention trials and preonset monitoring to reduce risk of severe complications and aiding in detection of environmental triggers (5). Third, multiple biomarkers and genetic variants have been shown to alter risk of T2D, revealing previously unsuspected biological pathways and providing new targets. Fourth, T2D has been shown to be a complex combination of multiple conditions and processes, defined by process-specific subgroups in which individuals with extreme burdens of risk in particular pathways reside and for whom a specific therapeutic approach may be optimal (6). Finally, the tools, resources, and data now exist to determine the biological and lifestyle/environmental predictors of drug response, as measured by a variety of clinical outcomes (7).

THE PRECISION MEDICINE IN DIABETES INITIATIVE

The idea of precision diabetes medicine is gaining momentum, based upon the promise of reducing the enormous and growing burden of diabetes worldwide. To address this, the Precision Medicine in Diabetes Initiative (PMDI) was launched in 2018 by the American Diabetes Association (ADA), in partnership with the European Association for the Study of Diabetes (EASD). The PMDI has partnered subsequently with other organizations (the U.S. National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] and JDRF).

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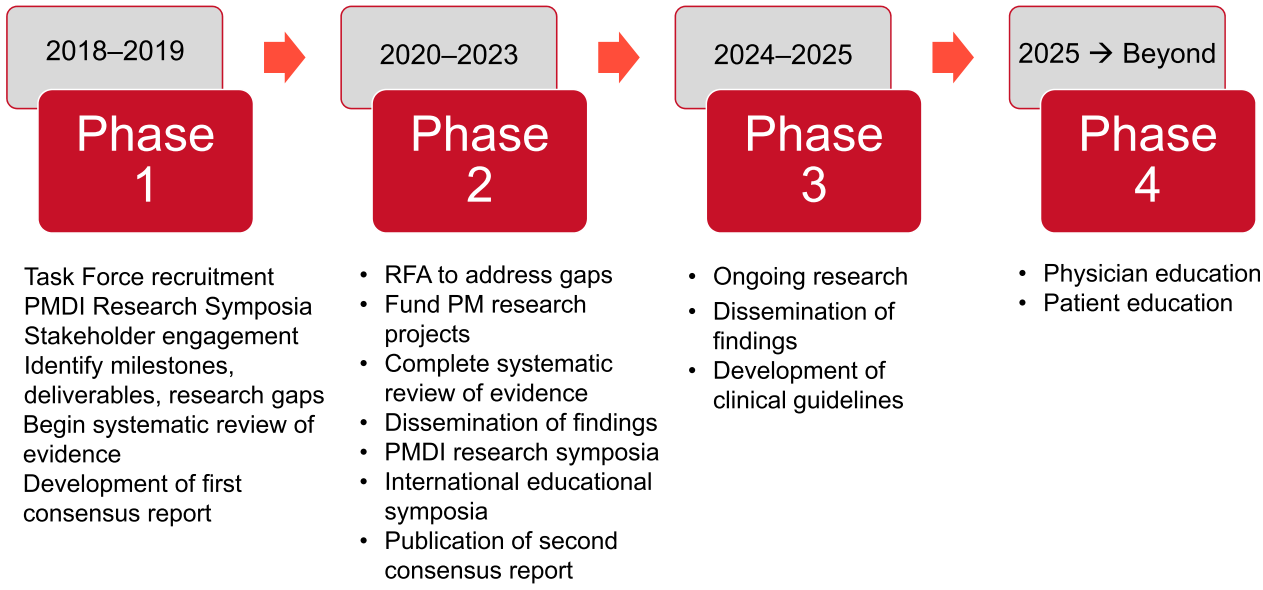

Figure 1—PMDI activities. PM, precision medicine; RFA, research funding announcement.

The mandate of the PMDI is to establish consensus on the viability and potential implementation of precision medicine for the diagnosis, prognosis, prevention, and treatment of diabetes, through expert consultation, stakeholder engagement, and systematic evaluation of available evidence. This mandate is pursued in order to realize a future of longer, healthier lives for people with diabetes.

The PMDI is focused on assessing evidence, promoting research, providing education, and developing guidelines for the application of precision medicine in diabetes. The 2019 ADA Scientific Sessions (held in June 2019) sponsored a research symposium focused on precision medicine, followed by a PMDI stakeholder meeting (held in October 2019) that was attended by experts in areas germane to precision diabetes medicine from around the world. Future PMDI symposia will extend the themes of precision diabetes medicine during the 2020 ADA Scientific Sessions and EASD Annual Meeting. In the coming years, educational approaches to translate the science into practice will be the target of a series of postgraduate education symposia. A global clinical research network focused on precision diabetes medicine is also being planned, along with other education and information dissemination activities (see Fig. 1 for an overview of key objectives).

The purpose of the work underlying the ADA/EASD PMDI consensus reports, of which this is the first, is to define relevant terminology (Text Box 1) and review the current status of diagnostics and therapeutics (prevention and treatment) in diabetes, including key areas of opportunity and where further inquiry is needed (Text Boxes 2–4). Particular focus is placed on elucidating the etiological heterogeneity of diabetes, which involves a combination of approaches including contemporaneous measures of risk factors, biomarkers, and genomics, as well as lifestyle and pharmacological interventions. Monogenic diabetes is one of few areas where precision diabetes medicine has been proven feasible and is practiced (as discussed at a recent *Diabetes Care* Editors' Expert Forum; M.C. Riddle, personal communication). This first Consensus Report does not seek to address extensively the role of precision medicine in the complications of diabetes, which is a topic for future evaluation. In addition, we do not discuss diabetes digital device technology, as this is addressed in a joint ADA/EASD consensus report (8,9). A second PMDI consensus report will be published documenting the findings of a systematic evidence review, focusing on precision diagnostics and precision therapeutics (prevention and treatment).

An *Executive Oversight Committee*, comprising representatives from the founding organizations, ADA (L.P.) and EASD (J.J.N.), and the two co-chairs of the initiative (P.W.F. and S.S.R.), provide PMDI governance. The Executive Oversight Committee is responsible for ensuring that the PMDI activities are executed. Leadership and direction of the PMDI are provided by members of the PMDI *Steering Committee*, currently composed of academic leaders in precision diabetes medicine from the U.S. (W.K.C., J.C.F., J.M.N.) and Europe (A.T.H., M.I.M., E.R.P.), a representative from NIDDK (C.G.L.), and the Executive Oversight Committee members (L.P., J.J.N., P.W.F., S.S.R.). The Steering Committee is responsible for providing guidance for PMDI activities and engages in developing precision diabetes medicine education, drafting consensus statements, and building interest/working groups to achieve its mission. The Executive Oversight Committee and the Steering Committee work closely together under the banner of the *PMDI Task Force*. Membership of the Steering Committee will expand to include experts from around the world and across multiple areas of expertise germane to the topic of precision diabetes medicine.

Work for this Consensus Report began at the October 2019 stakeholder meeting in Madrid. The meeting included presentations and roundtable discussions. At the conclusion of the meeting, a writing group meeting attended by the PMDI Task Force and stakeholders was held to determine what should be addressed in the Consensus Report. Following the meeting, consensus was reached by the PMDI Task Force through bimonthly calls and electronic

Text Box 1—Definitions

- ***Precision diagnosis*** involves refining the characterization of the diabetes diagnosis for therapeutic optimization or to improve prognostic clarity using information about a person's unique biology, environment, and/or context.
  - Precision diagnostics may involve subclassifying the diagnosis into subtypes, such as is the case in MODY, or utilizing probabilistic algorithms that help refine a diagnosis without categorization.
  - Careful diagnosis is often necessary for successful precision therapy, whether for prevention or treatment. This is true where subgroup(s) of the population must be defined, within which targeted interventions will be applied, and also where one seeks to determine whether progression toward disease has been abated.
  - Precision diagnosis can be conceptualized as a pathway that moves through stages, rather than as a single step. The diagnostic stages include *1*) an evaluation of prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex, and ancestry; *2*) probability based on clinical features; and *3*) diagnostic tests that are interpreted in the light of *1*) and *2*). A diagnosis in precision medicine is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth nor a permanent state.
- ***Precision therapeutics*** involves tailoring medical approaches using information about a person's unique biology, environment, and/or context for the purposes of preventing or treating disease (see *Precision prevention* and *Precision treatment*, below).
- ***Precision prevention*** includes using information about a person's unique biology, environment, and/or context to determine their likely responses to health interventions and risk factors and/or to monitor progression toward disease.
  - Precision prevention should optimize the prescription of health enhancing interventions and/or minimize exposure to specific risk factors for that individual. Precision prevention may also involve monitoring of health markers or behaviors in people at high risk of disease, to facilitate targeted prophylactic interventions.
- ***Precision treatment*** involves using information about a person's unique biology, environment, and/or context to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome, while reducing unnecessary side effects.
  - Today, the objective of precision therapy is to maximize the probability that the best treatment of all those available is selected for a given patient. It is possible that in the future, precision diabetes medicines will be designed according to the biological features of specific patient subgroups, rather than for the patient population as a whole.
- ***Precision prognostics*** focuses on improving the precision and accuracy with which a patient's disease-related outcomes are predicted using information about their unique biology, environment, and/or context.
  - The focus of precision prognostics includes predicting the risk and severity of diabetes complications, patient-centered outcomes, and/or early mortality.
- ***Precision monitoring*** may include the detailed assessment of biological markers (e.g., continuous glucose monitoring), behaviors (e.g., physical activity), diet, sleep, and psychophysiological stress.
  - Precision monitoring can be achieved using digital apps, cutaneous or subcutaneous sensors, ingestible sensors, blood assays etc.
  - The intelligent processing, integration, and interpretation of the data obtained through precision monitoring are key determinants of success.
  - Precision monitoring may be valuable for precision prevention (e.g., in T1D), precision diagnostics (e.g., where diagnoses are based on time-varying characteristics), and precision prognostics (e.g., where disease trajectories are informative of the development of key outcomes).

communication. Relevant experts outside of the Task Force were asked to contribute sections as needed. The Consensus Report was then peer reviewed by experts in the field and by the clinical committees of the founding organizations. The report was then submitted to *Diabetes Care* and *Diabetologia* for simultaneous publication.

PRECISION DIABETES MEDICINE: WHAT IT IS AND WHAT IT IS NOT

Precision diabetes medicine refers to an approach to optimize the diagnosis, prediction, prevention, or treatment of diabetes by integrating multidimensional data, accounting for individual differences (Text Box 1). The major distinction from standard medical approaches is the use of complex data to characterize the individual's health status, predisposition, prognosis, and likely treatment response. Precision medicine also focuses on identifying patients who, despite a diagnosis, do not require treatment (or require less than might conventionally be prescribed). These data may stem from traditional sources such as clinical records, as well as from emergent sources of "big data" such as individual medical records from very large cohorts of patients; geomobility patterns obtained from devices; behavioral monitors (e.g., actigraphy for exercise and sleep assessments); ingestible, subcutaneous, or wearable sensors (e.g., for blood glucose monitoring); and genomic and other 'omics data. Integration of patient preferences, patient-centered outcomes, cost-effectiveness, and shared decision making will guide how precision diabetes medicine is formulated and applied.

There are several terms sometimes used interchangeably with precision medicine, including "personalized medicine," "individualized medicine," and "stratified medicine." The 2020 ADA *Standards of Medical Care in Diabetes* (ADA SOC) places considerable emphasis on the personalization of diabetes medicine, highlighting that "clinicians care for patients and not populations" (10) (p. S2). This reflects the appreciation of individual differences with respect to symptomatology, presentation, behaviors, preferences, social circumstances, response to treatment, comorbidities, or clinical course. For precision diabetes medicine to be effective, it must be tailored to the individual. Thus, the ADA SOC instructs the clinician to adapt guidelines to each patient's characteristics, circumstances, and preferences, including the patient's food security, housing, and financial stability. In the context of the PMDI, this is not considered to be precision medicine; rather, this final step in the process of translating knowledge into practice is personalized (or individualized) medicine. In contrast, precision (or stratified) medicine emphasizes tailoring diagnostics or therapeutics (prevention or treatment) to subgroups of populations sharing similar characteristics, thereby minimizing error and risk while maximizing efficacy. Included within precision diabetes medicine is the monitoring of disease progression using advanced technologies or

Text Box 2—Precision diagnostics: background, barriers to implementation, and research gaps

- **Type 1 diabetes.** Best diagnostic results depend on integrating all diagnostic modalities, not by relying on prior prevalence, clinical features, or test results in isolation. The age at which the initial islet autoantibody appears and the type of autoantibody (e.g., which of the four primary antibodies among ICA512, insulin, GAD, and ZnT8) may be important in defining etiological subtypes of T1D. The majority of the genetic risk of T1D is now known, and the sensitivity and specificity of a T1D genetic risk score (T1D-GRS) both exceed 80%. Despite this, a high T1D-GRS will have low positive predictive value in patient populations where the overall prevalence of T1D is low, such as those aged >50 years when diabetes is diagnosed. It will likely prove most useful when the T1D-GRS is combined with clinical features and islet autoantibodies. At present, there is no immune-based test sufficiently reproducible and robust that it can be used diagnostically.
- **Type 2 diabetes.** Categories based on cluster analysis at diagnosis can provide insights into likely progression, risk of complications, and treatment response, which offer an exciting approach to subclassification of T2D. At this time, the available genetic data for T2D do not have sufficient predictive accuracy to replace existing delineative approaches. Although the subcategorization of T2D using genetic data is informative regarding the etiological processes that underlie the disease, the methods described so far (6,101) are not intended to be used to subclassify a T2D diagnosis nor are the existing genetic data sufficient for this purpose for the majority of individuals with T2D. Treatment response and progression can be predicted from clinical features (137). An advantage of using clinical features for diagnosis of T2D is that they are widely available and easily obtained (e.g., sex, BMI, HbA_{1c}); however, a potential limitation is that they may vary over time.
- **Barriers to implementation.** One of several important translational barriers facing the proposed clustering approach for T1D and T2D is that a fasting C-peptide measurement is required at the time of diagnosis, which is not routinely performed in clinical practice, and the reliability of C-peptide assays varies considerably between laboratories (41). Another limitation is that the biomarkers used to define these clusters change over time depending on the disease course or its treatment, such that this approach can only be applied to newly diagnosed individuals, but not to individuals years before disease onset or the many millions of people with long-standing diabetes worldwide. Moreover, the current approaches for clustering in T2D require continuously distributed data to be categorized, which typically results in loss of power. Thus, these methods do not yield good predictive accuracy, a major expectation in precision medicine, but this may change as the approach is refined.
- **Research gaps.** Based on limited ideal tests and uncertainty in etiology, more research is needed in T1D and T2D in order to define subtypes and decide the best interventional and therapeutic approaches.

considering how patient features affect the reliability of assays. The application of precision diabetes medicine may substantially reduce errors in diagnostic (Fig. 2), therapeutic (Fig. 3), and prognostic (Fig. 4) processes. For example, the interrogation of large sets of longitudinal clinical data could identify disease subtypes and match the patient to others with a similar disease profile; through knowledge of treatment efficacy and outcomes, more precise prognosis and optimization of therapies for this patient by concordance to similar subgroups would emerge (Text Box 1 and Figs. 3 and 4).

PRECISION DIAGNOSTICS

What are the Requirements for Precision Diagnosis?

Precision diagnostics (Text Box 2) employs methods to subclassify patients to enable the successful application of precision medicine approaches (Fig. 2). This will facilitate matching precise prevention strategies and treatments to individuals either at risk for or diagnosed with diabetes. Ideally, a precision diagnostic test should be *1*) robust (high test-retest reliability within and between laboratories); *2*) able to define a discrete subgroup giving insights into disease etiology, prognosis, and treatment response; *3*) widely available; *4*) easily performed with accepted norms for interpretation; *5*) inexpensive (or at least cost-effective); and *6*) approved by regulatory authorities.

Precision diagnosis can be conceptualized as a pathway that moves through stages, rather than as a single step. The diagnostic stages include assessing the:

- expected prevalence based on epidemiology, including age, or age at diagnosis of diabetes, sex, and ancestry,
- probable clinical diagnosis using clinical features and other data, and

Text Box 3—Precision prevention: background, barriers to implementation, and research gaps

- **Type 1 diabetes.** In T1D, precision prevention mainly involves the optimization of monitoring methods, thereby facilitating early detection and treatment. The reasons most prevention trials in T1D have not been effective may include failure to consider the individual's unique T1D risk profile (e.g., genetic susceptibility) and their unique response to the preventive agent (immune therapy or dietary intervention). Without considering the unique genetic profiles of children, interventions aimed at preventing type 1 diabetes (e.g., dietary intervention or immunotherapy) may be unlikely to succeed. Thus, precision prevention in T1D is likely to involve stratification of at-risk populations and innovative monitoring technologies.
- **Type 2 diabetes.** T2D has many avenues for prevention; thus, the possibilities for precision approaches, possibly through tailoring of diet, are broad. To date, prevention of T2D has focused on people with prediabetes. To be cost-effective, it will likely be necessary to stratify the population with prediabetes such that only those with other relevant risk factors are the focus of preventative interventions. Relevant risk factors may include lifestyle, socioeconomic status, family history, ethnicity, and/or certain biomarker profiles, including genetics.
- **Barriers to implementation.** The effective implementation of precision prevention will require that appropriate technologies are available, the general public has the willingness to embrace the approach and that those in greatest need can access precision prevention programs. A communication plan used by the interventionalist and the patient's perception of risk should be a focus of precision prevention strategies.
- **Research gaps.** There are critical areas of research required for implementation of precision prevention in diabetes, including determining for whom online care is more effective than in-person care, the types of staff delivering the lifestyle modification programs, the impact of group and/or individual interaction, and the frequency of such sessions. There is also uncertainty about how best to provide and sustain lifestyle modification. In addition, emphasis should be placed on identifying profiles that indicate the likely response to specific lifestyle interventions (focusing on specific diets, exercise programs, and other behavioral factors) and sensitivity to risk factors (such as sleep disturbance, stress, depression, poor diet, sedentary behaviors, smoking, certain drugs, and obesity).

Text Box 4—Precision medicine approaches to treat diabetes: background, barriers to implementation, and research gaps

- **Type 1 diabetes.** The only existing therapy is insulin for T1D. Developments in long-acting and glucose-sensitive insulins are improving the health and well-being of people with T1D, as are technological advances in continuous glucose monitoring devices, insulin pumps, closed-loop systems, and the artificial pancreas.
- **Type 2 diabetes.** It has long been recognized that T2D is heterogeneous in its etiology, clinical presentation, and pathogenesis. Yet, traditionally, trials of therapeutic intervention do not recognize this variation.
- Monogenic forms of diabetes are already amenable to precision treatment, if correctly diagnosed. For example, *HNF1A*-MODY (MODY3), *HNF4A*-MODY (MODY1), and *ABCC8*-MODY (MODY12) are acutely sensitive to the glucose-lowering effects of sulfonylureas. Alternatively, individuals with *GCK*-MODY (MODY2) can have unnecessary treatments stopped.
- With increasing efforts to map patients with T2D in etiological space using clinical and molecular phenotype, physiology, and genetics, it is likely that this increasingly granular view of T2D will lead to increasing precision therapeutic paradigms requiring evaluation and potential implementation. Genetic variation not only can capture etiological variation (i.e., genetic variants associated with diabetes risk) but also variation in drug pharmacokinetics (absorption, distribution, metabolism, and excretion [ADME]) and in drug action (pharmacodynamics).
- In contrast, "true" T2D is a common complex disease characterized by thousands of etiological variants, each contributing to a small extent to diabetes risk. Thus, it remains uncertain that genetic variants will be identified that are highly predictive of drug outcomes in T2D, even if process-specific polygenic risk scores are derived (where all variants on an etiological pathway are combined to increase power).
- **Barriers to implementation.** The current and growing burden of diabetes is not from western white populations but from other ethnic groups, in particular South and East Asians. Yet, these populations are underrepresented in clinical trials and, in particular, in attempts to understand variation in drug outcomes.
  - Because the diabetes phenotype can vary markedly by ethnic group, it is likely that complications and drug outcomes will differ between populations.
  - Many of the approaches gaining traction in precision medicine generate massive data sets that are burdensome to store and require powerful computational servers for analysis.
  - Undertaking appropriately designed clinical trials for precision treatments that meet the current expectations of regulatory authorities may be challenging, given the many subgroups within which treatments will need to be evaluated. Innovative clinical trials will likely be needed and real-world evidence will likely need to be part of the evaluation process.
  - Translating complex information to patients about genetic (and other 'omics) tests in a clear, concise, and clinically relevant manner will require health care providers to be appropriately trained.
- **Research gaps.** For drug outcomes, there is a pressing need to move beyond early glycemic response and examine variation in response in terms of cardiovascular outcomes and mortality rates, especially of the newer agents such as SGLT2i and GLP-1RA, with focus on specific patient subgroups. Identifying predictive markers (especially genetic markers) of serious adverse events in patients treated with these drugs presents an additional area urgently in need of greater attention.
  - Need for functional studies to determine the mechanism(s) of action underlying specific gene variants
  - Need for better understanding of the pathophysiology of diabetes to inform on new therapeutic targets
  - Need to study broader populations/ethnic groups
  - Need for understanding outcomes of highest relevance to patients
  - Need for decision-support tools to implement precision diabetes medicine in clinical practice
  - Need to demonstrate that approaches are cost-effective

- modification by diagnostic tests that are interpreted in the light of prevalence and diagnosis.

A diagnosis in precision medicine is a probability-based decision, typically made at a point in the natural history of a disease, reflecting neither an absolute truth nor a permanent state. Presenting the degree of uncertainty in a manner that is intuitive to the patient and practitioner is critical if the precision diagnosis is to be effective.

Precision Diagnosis in Clinical Practice

Interpreting HbA_{1c} in Diagnosis and Monitoring

Data and outcomes from the widespread use of glycated hemoglobin (HbA_{1c}), rather than blood glucose levels, for diagnosis has led to a precision approach for the diagnosis of diabetes. The level of HbA_{1c} will depend on factors that impact hemoglobin and red cell stability as well as average glucose values (10). Genetic testing can reveal unsuspected variants that alter HbA_{1c}. Thus, knowledge of the patient's ancestry and specific genetic information can guide interpretation of assay results for diagnosis and the monitoring of blood glucose.

Diagnosing T1D Versus T2D

Currently, the most common step toward precision diagnosis that is made in clinical diabetes medicine is the classification of T1D versus T2D, the two most prevalent subcategories with different etiologies and different treatment requirements. Part of the diagnostic dilemma is that neither T1D nor T2D are monolithic entities and robust "gold standards" are not universally agreed. Diagnostic issues arise when expected clinical features are discordant from established norms (e.g., people diagnosed with diabetes who are young and have obesity, or old and slim, or who are a rare subtype in that clinical setting) (11). Islet autoantibody positivity varies by clinical setting (e.g., in people without diabetes, individuals diagnosed with probable T1D as children, individuals with clinical features of T2D), resulting in an altered prior probability of T1D that reflects the different prevalence in these diverse settings. The best diagnosis depends on integrating all diagnostic modalities, as demonstrated in predicting long term C-peptide negativity in individuals diagnosed with diabetes between 20 and 40 years of age, where an integrated model outperformed diagnosis based on clinical features, circulating antibodies, or genetics used in isolation (3). The frequency of misdiagnosis of T1D and

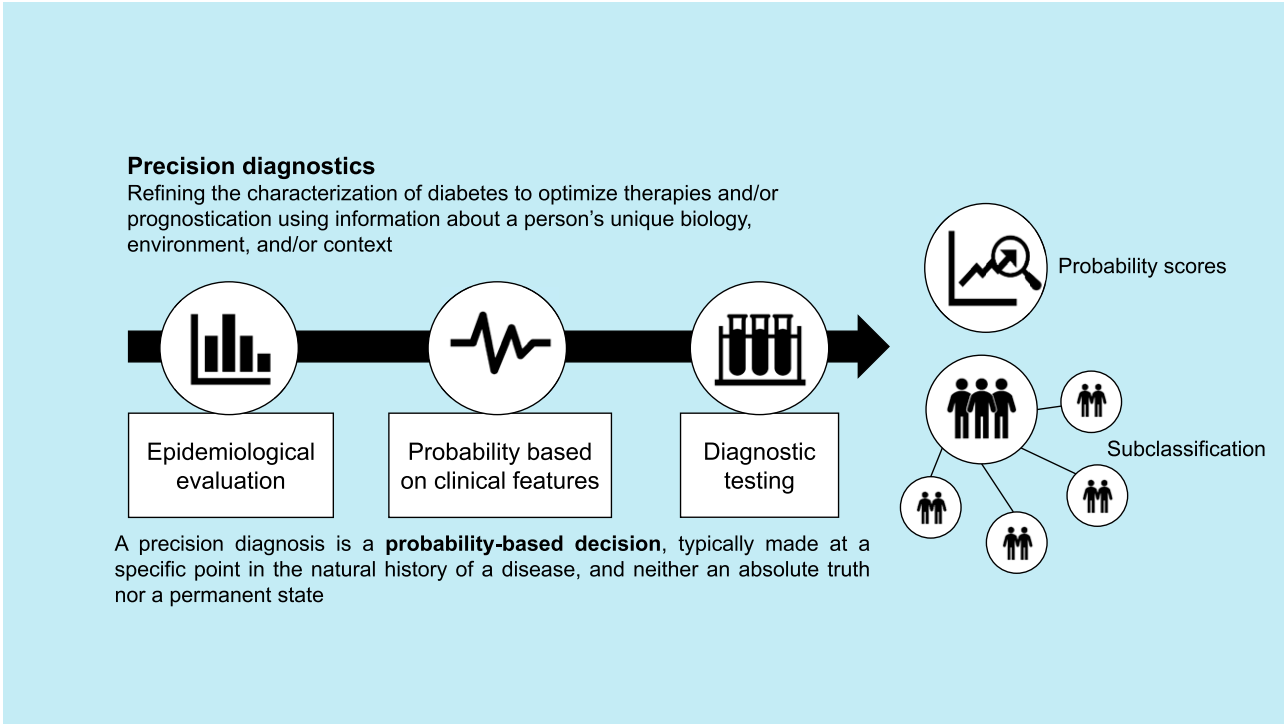

Figure 2—Precision diagnostics

T2D in middle-aged and elderly adults (11,12) suggests that precise diagnostic approaches are needed, especially as failure to recognize insulin-deficient states can be fatal.

Monogenic Diabetes

A *Diabetes Care* Editors' Expert Forum (M.C. Riddle, personal communication) has concluded recently that a monogenic diabetes diagnosis is closest to meeting all criteria for a perfect diagnostic test as it defines a discrete subgroup giving insights into etiology, prognosis, and treatment response (1,2). Most cases of monogenic diabetes remain misdiagnosed. Perhaps the best example of precision diabetes medicine is the excellent and long-lasting glycemic response to oral sulfonylureas in insulin-dependent infants diagnosed with neonatal diabetes caused by abnormalities in the β-cell potassium channel (13–17). In *GCK*-MODY (MODY2), it is established that patients do not require (18), or respond to, oral medication (19). Other MODY diagnoses (*HNF1A* [MODY3], *HNF4A* [MODY1] and *ABCC8* [MODY12]) are acutely sensitive to the glucose-lowering effects of sulfonylureas (20–22); however, unless the diagnosis is precise, these therapeutic benefits are lost. With the clear benefits of precision diagnosis of monogenic diabetes, it is important to reduce barriers to its implementation. For example, the cost of performing molecular genetic testing is high and universal testing is not cost-effective. It is thus necessary to limit testing to those most likely to have a monogenic diagnosis. Moreover, identification protocols require prescreening based on clinical features (e.g., family history, age at onset, phenotype including syndromic features) and nongenetic testing (islet autoantibodies and C-peptide).

One approach for implementing precision medicine in the case of monogenic diabetes would be to:

- test all infants diagnosed with diabetes in the first 6 months of age, because >80% have a monogenic cause of neonatal diabetes;
- use a MODY calculator to identify those whose clinical features suggest a high likelihood of MODY (www.diabetesgenes.org/mody-probability-calculator/) (23);
- test individuals with pediatric diabetes when at least three islet autoantibodies are antibody negative (24).

The effective use of these pregenetic selection criteria should greatly improve the likelihood of correctly diagnosing monogenic diabetes without the burden of costly genetic screens. Although diagnostic molecular genetic testing utilizes robust analysis of germline DNA, which is virtually unchanged throughout life, there are still issues with its implementation. One issue is the incorrect interpretation of the genetic information, leading to inaccurate identification of causal mutations in both clinical practice and in the published research literature (25). Curation of pathogenic variants for monogenic diabetes is critical and is currently being addressed by international consortia. As a result of technological advances, multiple causes of monogenic diabetes can be tested for in a single next-generation sequencing test. This approach is generally advantageous as it does mean that syndromic monogenic diabetes is diagnosed genetically when the patient presents with isolated diabetes. This will allow other features to be examined and treated appropriately before clinical presentation. Examples of this are neonatal diabetes (2), *HNF1B*-MODY (MODY5) (26), *WFS1* (Wolfram syndrome) (27), and mitochondrial diabetes (28). For these patients, the genetic diagnosis of diabetes will have implications far beyond the prognosis and care of diabetes, as the patient

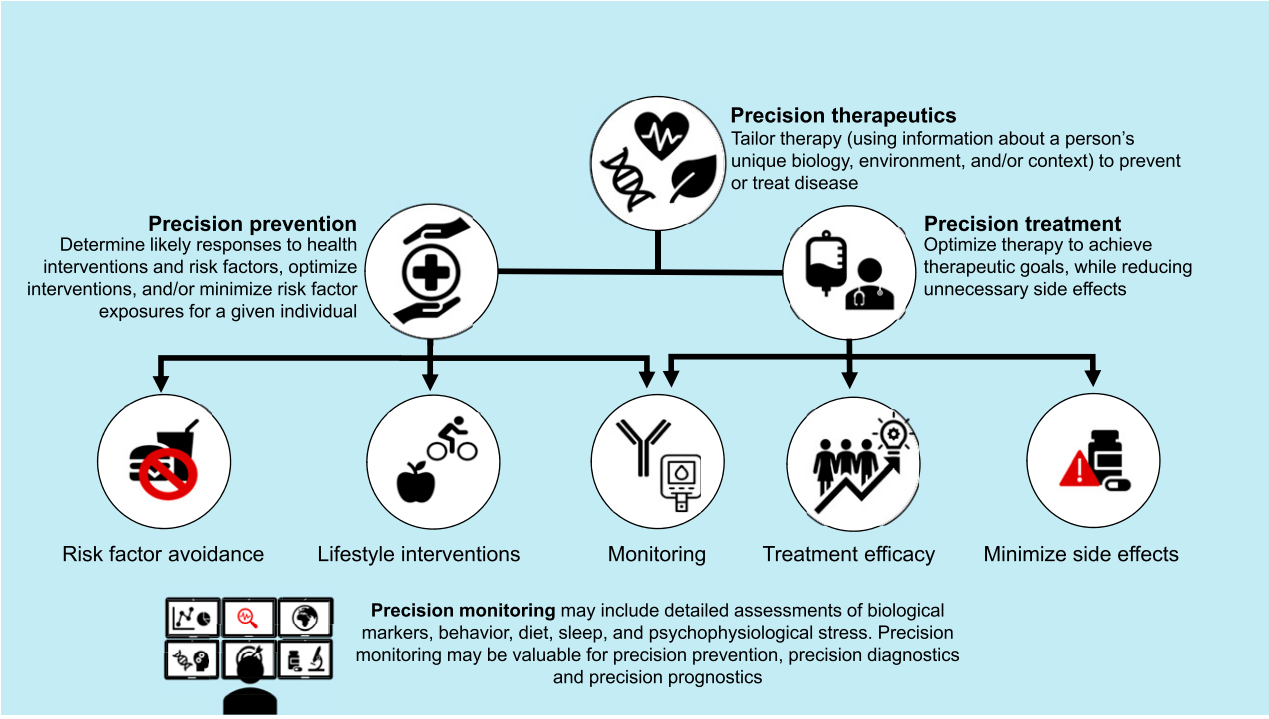

Figure 3—Precision therapeutics

with certain types of monogenic diabetes will also be at high risk of developmental delay, neurological disease, developmental kidney disease, liver failure, deafness, and cardiomyopathy.

Diagnosing Latent Autoimmune Diabetes in Adults

Latent autoimmune diabetes in adults (LADA) is not currently recognized by the ADA as a formal subtype of diabetes. Nevertheless, LADA reveals some of the difficulties in diabetes subtyping. It was shown that the presence of GAD autoantibodies in patients with T2D was associated with progression to early insulin therapy (29); yet, controversy remains as to whether LADA is a discrete subtype, a milder form of T1D, or a mixture of some patients with T1D and others with T2D. The uncertainty is increased by variation in the diagnostic criteria, with initial treatment based upon physician preference as well as the patient's presentation (30). In addition, among those with GAD autoantibodies, the phenotype varies with different autoantibody levels (31).

Subcategories of Common Forms of Diabetes

The subcategorization of T1D or T2D may not always be the optimal approach for precision diabetes diagnosis or therapy. Nevertheless, the ability to delineate T1D or T2D using nontraditional data and approaches may lead to improvements in prevention or treatment of the disease, including diabetes subclassifications beyond T1D or T2D.

Subcategories in T1D. The age at which the initial islet autoantibody appears and the type of autoantibody (e.g., which of the four primary antibodies among islet cell autoantigen 512/islet antigen 2 [ICA512/IA-2], insulin, GAD, zinc transporter 8 [ZnT8]) may be important in defining etiological subtypes of T1D (32). Data supporting this potential subcategory are based upon those diagnosed in the first 10 years of life and in predominantly white European populations. The relevance to other ethnic groups and those diagnosed later in life is uncertain.

The genetic variants accounting for the majority of risk of T1D are now known, and the sensitivity and specificity of T1D genetic risk scores (T1D-GRS) both exceed 80% (5,33–35); however, a high T1D-GRS will have low positive predictive value in populations with a typically low prevalence. A T1D-GRS may prove most useful when integrated with clinical features and islet autoantibodies (3,4). There is variation in the genetic susceptibility with age at diagnosis but, at present, genetics is not suggested as an approach for defining subtypes of T1D.

There is strong evidence for enrichment of immune cell types that are associated with genetic risk of T1D, particularly T cells ($CD4^+$ and $CD8^+$) and B cells ($CD19^+$). However, at present, there is no immune-based test sufficiently reproducible and robust that it can be used diagnostically for T1D.

Persistent endogenous β-cell function in T1D is associated with greater potential for improved glycemic control and reduced complications (36). A stimulated C-peptide measurement represents a candidate for defining subcategories of T1D with different treatment aims. C-peptide levels exponentially fall in the "honeymoon period" after T1D diagnosis (37) but have been shown to be stable 7 years after diagnosis (38). Persistent C-peptide is associated with a later age of diagnosis, although there are few data to predict those likely to maintain high levels of C-peptide.

Subcategories in T2D. Family history of T2D, as a surrogate for precise genetic evaluation, fails to meet many of the criteria of a robust test as any assessment changes over time and depends on the relatives selected for reporting the "family." The value of a family history may be

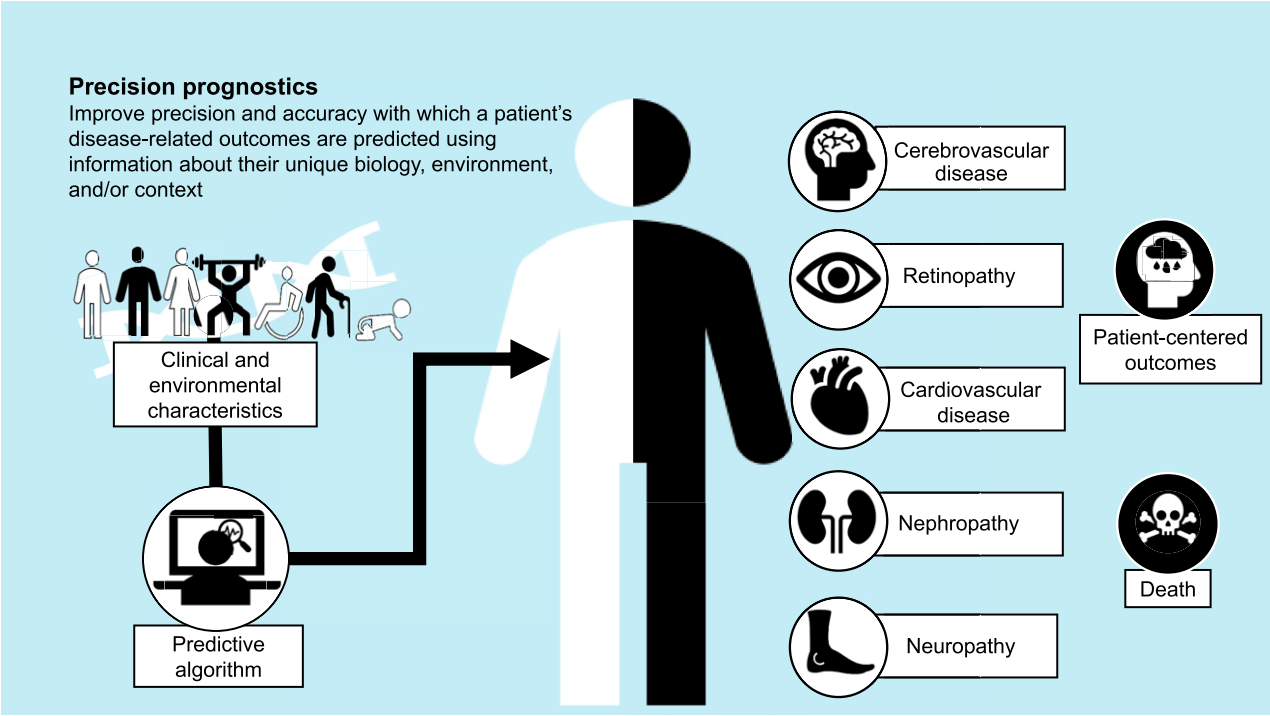

Figure 4—Precision prognostics

greatest in monogenic diabetes, in which a pedigree will often demonstrate a pattern of inheritance consistent with a single gene disorder and a consistent phenotype.

T2D treatment response and disease progression can be predicted from continuous clinical features with specific models. These models appear to perform better than dividing into cluster-based subgroups (7). An advantage of using clinical features is that they are widely available and easily obtained (e.g., sex, BMI, HbA_{1c}). However, they are limited by the fact that clinical features may vary over time and with the natural history of the disease. Incorporation of longitudinal change with treatment response could be a strength as the model's prediction would change in concert with changes in the phenotype of the patient.

Recent research has attempted to define subcategories of T2D (and T1D) based on cluster analysis at diagnosis to provide insights into likely progression, risk of complications, and treatment response (39,40). Barriers facing this and other approaches include collection of data that are not routinely obtained (e.g., a fasting C-peptide at the time of diagnosis, with considerable variation in results between laboratories [41]) and the change in biomarkers over time that are dependent on disease course or its treatment. Genetic data have been used to define T2D subcategories by clustering genetic variants that associate with physiological traits and which are correlated with clinical outcomes (6). At this time, the available genetic data for T2D and the clustering does not have sufficient predictive accuracy to replace existing delineative approaches. None of the methods described above are established for subclassification of T2D in clinical practice; nevertheless, it is true that in a minority of patients, their specific type of diabetes may be adequately characterized using genetic clustering (42,43).

PRECISION THERAPEUTICS

Accurate diagnosis is necessary for successful precision therapy, whether for prevention or treatment (Fig. 3). This is true where subgroup(s) of the population must be defined to determine which targeted interventions will be applied, as well as for determination of treatment outcome. In monogenic diabetes, there are no currently known options for prevention. In T1D, precision prevention currently involves mainly the optimization of monitoring methods (Text Box 3), thereby facilitating timely early detection, preventing early complications and allowing appropriate treatment. In contrast, T2D has many avenues for prevention; thus, the possibilities for precision approaches, possibly through tailoring of lifestyle (e.g., diet), are broad in T2D.

Precision Prevention in Diabetes (Text Box 3)

Type 1 Diabetes

T1D is characterized by damage, impairment, and eventual destruction of the insulin-producing pancreatic β-cells, thought to be the result of an autoimmune process. T1D progression has been grouped into discrete "stages" (44). Stage 1 is defined by the presence of ≥2 islet autoantibodies, with normal blood glucose; stage 2 is defined by the presence of ≥2 islet autoantibodies with elevation of blood glucose, signaling the functional impairment of the β-cells; and stage 3 is characterized by symptoms of dysglycemia, such as polyuria or diabetic ketoacidosis, although not all symptoms need be present. A clinical diagnosis of T1D typically is not given until stage 3. T1D is nearly inevitable once ≥2 islet autoantibodies appear, particularly in those of younger age, with a lifetime diabetes risk approaching 100% (45,46). Approximately half of the risk of T1D is due to genetic factors, with over 30% of

Text Box 5—Precision medicine approaches to lessen treatment burden and improve quality of life

- **Diagnosis and disease management.** A more specific diagnosis has the potential to reduce uncertainty and manage future expectations about disease course. This is clearly the case for some monogenic forms of diabetes, where diagnosis is nearly certain, given its strong genetic indication, and the specific treatment is coupled to the subcategory (genetic subtype) of disease. Emerging knowledge regarding subtypes of T2D indicates that there is potential to classify individuals with diabetes at risk for progression to complications.
- **Misdiagnosis.** Inaccurate classification of the type of diabetes, either from lack of precision or inadequate clinical attention to detail at the time of presentation, can have long-lasting, adverse effects on mental health and quality of life. In the pediatric and younger adult population, the risk of misclassification is increasing as both "true" T1D and "true" T2D classifications are confused through the growing obesity epidemic in youth (T2D) and older ages at onset (T1D). In addition, monogenic variants of diabetes can be misdiagnosed as either T1D or T2D. A precision approach to diagnosis with appropriate standardized laboratory support and increased research to obtain novel biomarkers of disease has the potential to solve this problem.
- **Complications.** Worry about complications is an issue for all people with diabetes. Currently, people with diabetes (either T1D or T2D) are given a label of being unequivocally at risk for reduced life span, amputation, kidney failure, and blindness. A more precise diagnosis, prognosis, and strategy to predict and prevent complications has the potential to greatly reduce disease burden and distress and improve quality of life. Nevertheless, there is also a risk that more precise prognostification may cause distress if the options for successful intervention are limited or incompatible with the patient's needs or desires.
- **Stigmatization.** A major burden for people with diabetes is that the disease is often considered the fault of the patient. This is particularly true for T2D, as it is often labeled as "just" a lifestyle disease. Clinical care of those with diabetes often results in a singular approach to treatment, regardless of their specific needs, life situation, and other conditions. A clinical process that makes diagnosis more precise and includes a patient-oriented evaluation and response to needs has the potential to lessen stigma and reduce associated distress.

the genetic risk attributable to genes of the human leukocyte antigen (*HLA*) complex but also including more than 50 non-*HLA* loci (35). Unknown environmental factors are thought to trigger the autoimmune process that results in initial β-cell damage and progression toward symptomatic T1D (47).

Primary prevention trials in genetically susceptible individuals who have not yet developed autoantibodies (i.e., prestage 1) and secondary prevention trials in children with stages 1 and 2 have been conducted (48) using dietary interventions and immune-targeting approaches. Dietary manipulation studies have been largely unsuccessful in reducing islet autoimmunity (49–51) or T1D (52). Previous intervention studies among individuals at stage 1 or stage 2 have been unable to slow, halt, or reverse the destruction of insulin-producing β-cells. Of nine completed secondary prevention trials (53–60), only one (using an anti-CD3 antibody) has shown a slight delay in progression to T1D (61).

Most prevention trials in T1D have not been effective, partially because the unique T1D genetic risk profile of the individual and their unique response to the preventive agent (immune therapy or dietary intervention) have not been considered. For example, the inflammatory response to infection with enteroviruses implicated in the onset of T1D has been shown to be genetically mediated (62) and diet has had different effects on development of autoimmunity and progression to T1D (63) dependent on genetic risk. Several studies have suggested that susceptibility to islet autoimmunity and progression to T1D may be related to the ability to adequately use vitamin D, as higher cord blood 25-hydroxyvitamin D was associated with a decreased risk of T1D, but only in children who were homozygous for a vitamin D receptor gene (*VDR*) variant (64). Risk of islet autoimmunity was observed with reduced dietary intake of the n-3 fatty acid α-linolenic acid, but only in those with a specific genotype in the fatty acid desaturase gene (*FADS*) cluster (65). Thus, without considering the unique genetic profiles of children, dietary supplementation may not be successful, arguing for an appropriately validated precision approach.

Type 2 Diabetes

The emergence of T2D as a global public health crisis during recent decades has motivated numerous large randomized controlled trials assessing the efficacy of pharmacological or lifestyle interventions for prevention. An emphasis has been placed on intervening in people with "prediabetes," defined as a person with levels of fasting blood glucose, 2-h blood glucose, or HbA_{1c} that are chronically elevated but below the diagnostic thresholds for diabetes. Although prediabetes is a major risk factor for T2D and other diseases (66), intervening in everyone with prediabetes may not be cost-effective (67). Aggressive precision prevention in those with relevant risk factors is discussed in the current ADA SOC (68). Youth with prediabetes should be the focus of preventive interventions, especially those with overweight or obesity and who have one or more additional risk factors (e.g., maternal history or exposure to gestational diabetes mellitus [GDM], a positive family history of diabetes in first- or second-degree relatives, signs of insulin resistance, or specific high-risk ancestry).

Multiple interventions in adults with T2D have been evaluated for risk reduction and prevention, both in the short and the long term. A recent systematic review (69) reported that after active interventions lasting from 6 months to >6 years, relative risk reduction achieved from lifestyle interventions (39%) was similar to that attained from use of drugs (36%); however, only lifestyle interventions had a sustained reduction in risk once the intervention period had ended. Analysis of the postintervention follow-up period (~7 years) revealed a risk reduction of 28% with lifestyle modification compared with a nonsignificant risk reduction of 5% from drug interventions.

Most lifestyle intervention programs use standardized approaches designed to change diet and exercise habits for reducing body weight. The Diabetes Prevention Program (DPP) evaluated the efficacy of lifestyle intervention and metformin therapy, compared with standard of care and placebo (control), for delay or prevention of diabetes in those with impaired glucose regulation at baseline. Although the reductions in diabetes risk from lifestyle (58% reduction) and metformin (31% reduction) compared

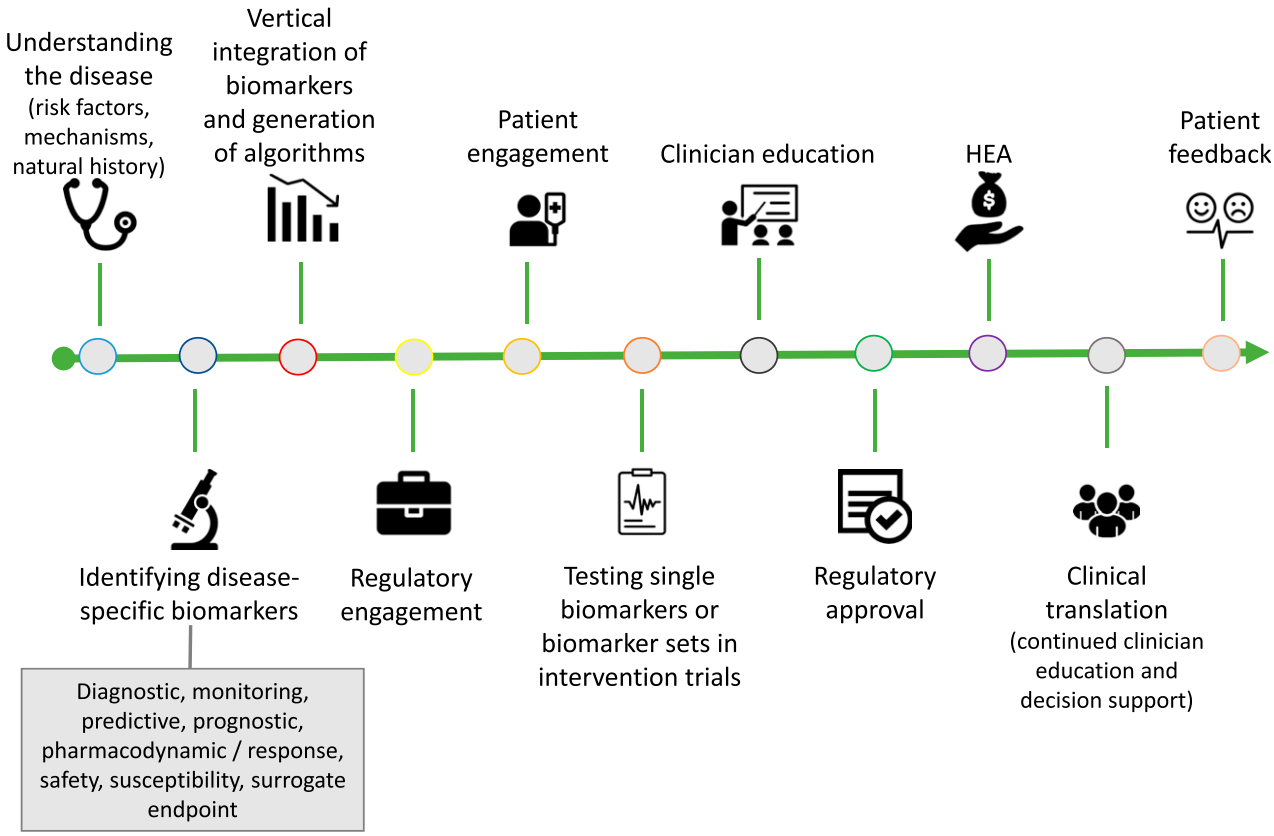

Figure 5—The path to precision diabetes medicine. HEA, health economic assessment. Adapted from Fitipaldi et al. (136).

with the control intervention were impressive (70), there was considerable variation across the study population (71), with many participants developing T2D during the active intervention period (the first 2.8 years of the trial). Thus, the DPP lifestyle intervention did not truly "prevent" diabetes. Indeed, in the decade after randomization, during which participants were offered lifestyle reinforcement semiannually, the average duration before disease onset was ~3 years (72). Those participants in the DPP who progressed most rapidly were those who lost the least weight in the early stages of the intervention (73), with genetic variants representing significant predictors of peak weight loss and weight loss maintenance (74). Results from the DPP and other large prevention trials suggest that a "one-size-fits-all" lifestyle intervention strategy will not be efficacious for everyone, particularly if it cannot be sustained, strengthening the case for precision lifestyle interventions in T2D prevention.

Although precision diabetes medicine is much more than genetics, the majority of relevant research has focused on evaluating the role of genetic variants in precision prevention. Large epidemiological studies (75) and intervention trials (76,77) strongly suggest that standard approaches for lifestyle modification are equally efficacious in preventing diabetes regardless of the underlying genetic risk. This contrasts with the extensive epidemiological evidence suggesting that the relationship of lifestyle with obesity is dependent on genetic risk (78–81); however, with few exceptions (e.g., [74]), analyses in large randomized controlled trials have failed to show that these same genetic variants modify weight loss in response to lifestyle intervention (82). It is also important to recognize that knowledge of increased genetic risk for diabetes may not motivate improvements in lifestyle behaviors. Indeed, knowledge of increased genetic risk for diabetes may decrease motivation to modify behavior in genetic fatalists (83).

Diet recommendations optimized to the individual have been shown to reduce postprandial glycemic excursions to a greater extent than standard approaches in healthy individuals (84). Meal compositions that induce the most favorable glycemic profiles have been guided by models derived from an individual's biological data (e.g., microbiome, genome, and metabolome), information on lifestyle factors (e.g., sleep and exercise), and postprandial glycemia following the consumption of a series of standardized meals. Although these studies indicate that personalized diet plans may help minimize postprandial glycemic excursions, no studies have reported the long-term impact of adhering to personalized diets on glycemic control.

Of the 12 approved classes of diabetes drugs, many having been assessed for efficacy in prevention. Overall, drugs that enhance insulin action have proven more effective in diabetes prevention than those that increase insulin secretion. Some of the variability in the diabetes-reducing effect of metformin in the DPP has been associated with variation in the *SLC47A1* gene that encodes the multidrug and toxin extrusion 1 (MATE1) transporter protein (85). In the DPP Outcomes Study, the effects of lifestyle, metformin, and placebo interventions on weight reduction during the 6–15

years that followed the end of the randomized intervention phase were assessed (86). As a percentage of baseline weight, those assigned to metformin maintained an average weight loss of 6.2% compared with the lifestyle intervention group, which maintained a weight loss of 3.7%, and the placebo group, which maintained a weight loss of 2.8%. In the subgroup of DPP participants who lost <5% baseline weight at 1 year post-randomization (poor responders), body weight during the following 14 years remained essentially unchanged, whether receiving metformin or placebo interventions. In contrast, those participants in the lifestyle intervention group who lost <5% baseline weight gained and sustained ~2 kg excess body weight in the years that followed. These findings reveal a subgroup of DPP participants in whom lifestyle intervention led to weight gain, which presents a potential avenue for stratified intervention, where individuals who are unlikely to respond well to lifestyle modification might be better served by other therapeutic approaches.

Precision Treatment (Text Box 4)

Once diabetes develops, a variety of therapeutic steps may be clinically indicated to improve disease management. These steps include:

- glucose monitoring
- patient education and lifestyle intervention (87)
- surgery
- drug treatments to lower HbA_{1c}
- drug treatments to lower cardiovascular risk (e.g., statins, antihypertensives)
- drug treatments targeting specific complications (e.g., ACE inhibitors/angiotensin II receptor blockers [ARBs] and sodium–glucose cotransporter 2 [SGLT2] inhibitors for proteinuric kidney disease, fibrates for retinopathy, atypical analgesics for painful neuropathy, and statins and antihypertensives for cardiovascular disease)

For each of these treatments, there will be patients who respond well and those who respond less well, in addition to those who have adverse outcomes from the therapy. Thus, precision treatment can be considered as using patient characteristics to guide the choice of an efficacious therapy to achieve the desired therapeutic goal or outcome while reducing unnecessary side effects (Fig. 3). Given the broad scope of precision treatment, pharmacological therapy in T2D has the best evidence base for precision therapeutics at present.

Subcategories and Drug Outcomes

Traditionally, trials of therapeutic interventions do not recognize variation in etiologic processes that lead to development of T2D. The MASTERMIND consortium recently reanalyzed data from the A Diabetes Outcome Progression Trial (ADOPT) and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) studies in order to highlight how clinical phenotype can be used to help guide treatment intervention. In ADOPT, on average, men without obesity showed a greater HbA_{1c} reduction over 5 years with sulfonylureas than they did with thiazolidinediones; however, women with obesity treated with thiazolidinediones had sustained HbA_{1c} lowering over the 5 years compared with sulfonylureas (88). When considering the clinical and physiological variables used to subgroup individuals with diabetes (39), the insulin-resistant cluster defined in ADOPT and RECORD responded better to thiazolidinediones while the older patient cluster responded better to sulfonylureas (7).

Similar studies have been undertaken to investigate how simple clinical variables can be used to predict glycemic response to dipeptidyl peptidase 4 inhibitors (DPP4i). In studies undertaken using prospective (Predicting Response to Incretin Based Agents in Type 2 Diabetes study [PRIBA]) and primary care data in the U.K. (Clinical Practice Research Datalink [CPRD]), an insulin-resistant phenotype of obesity and high triacylglycerols was associated with reduced initial response to DPP4i and more rapid failure of therapy (89).

As outlined under PRECISION DIAGNOSTICS and elsewhere (the upcoming Expert Forum), the most current examples of how genetics impacts precision treatment can be seen in monogenic diabetes, for which single gene mutations are causal for the development of diabetes and for which targeted treatments can, in effect, bypass the etiological defect (e.g., sulfonylurea sensitivity in *HNF1A*-MODY [MODY3] [20] and insulin independence with high-dose sulfonylureas in neonatal diabetes due to K_{ATP} channel defects [14]). In some instances, precision treatment may result in cessation of unnecessary medication, as is the case in people with *GCK*-MODY (MODY2), where blood glucose remains somewhat elevated, but stable, over time.

Unlike monogenic forms of diabetes, T2D is a common complex disease characterized by thousands of etiological gene variants. It is uncertain whether individual genetic variants will be highly predictive of drug outcomes. Similar to the underlying genetic architecture of T2D, it is possible that drug response in T2D will be influenced by many genetic variants of small to modest effect. Genetic studies of drug response in T2D have largely been based on candidate genes of known etiological processes or drug pathways. These studies have been limited in their success. For example, some studies have shown that the *KCNJ11/ABCC8* E23K/S119A risk variant increases glycemic response to sulfonylureas (90–92); in contrast, the *TCF7L2* diabetes risk variant reduces glycemic response to sulfonylureas (93–95). The *PPARG* Pro12Ala diabetes risk variant has been associated with reduced glycemic response to thiazolidinediones (96–98).

Genome-wide association studies (GWAS) have the potential to provide novel insights as they make no assumptions about drug mechanism or disease process, in contrast to candidate gene/pathway studies. Only GWAS of metformin have been reported to date (99,100), identifying that variants at the *ATM/NPAT* and *SLC2A2* loci are associated with an altered glycemic response. In *SLC2A2*, the noncoding rs8192675 variant C allele is associated with greater response to metformin and is associated with reduced expression of the SLC2A2 transporter in liver, intestines, and kidneys. In individuals with obesity, those with two copies of the C allele had an absolute HbA_{1c} reduction of ~1.55% (compared with a reduction of ~1.1% in those without the C allele). While this may appear to be a small difference, the *SLC2A2* genotype effect is the equivalent of a difference in metformin dose of 550 mg, or about half the average effect of starting a DPP4i.

When considering etiological variation, recent work partitioning diabetes-associated genetic variants by their presumed etiological process (partitioned polygenic scores) (6,42,101) may define genetically driven dominant processes. These processes, such as β-cell dysfunction, lipodystrophy, or obesity, could respond differently to drugs that act on these pathways, such as sulfonylureas, glucagon-like peptide 1 receptor agonist (GLP-1RA), DPP4i, and thiazolidinediones.

Genetic variation can not only capture etiological variation but also variation in drug pharmacokinetics (absorption, distribution, metabolism, excretion [ADME]) and in drug action (pharmacodynamics). Studies of ADME genes have revealed some variants with a moderate to large effect. For example, the 8% of the white population who carry two loss-of-function variants in *CYP2C9* are 3.4 times more likely to achieve HbA_{1c} target than those with normal function cytochrome P450 family 2 subfamily C member 9 (CYP2C9) due to reduced metabolism of sulfonylureas and increased serum concentrations (102). *SLCO1B1* and *CYP2C8* genotypes that alter liver uptake and metabolism of rosiglitazone can alter glycemic response (HbA_{1c}) by as much as 0.7% (103). While these studies have promoted pharmacogenetic approaches in precision diabetes therapeutics, some studies have been surprisingly negative. For example, loss-of-function variants in the *SLC22A1* gene, encoding the organic cation transporter 1 (OCT1), which transports metformin into the liver (104,105), do not reduce the glucose-lowering efficacy of metformin in patients with T2D (106,107). Thus, there is genetic evidence that metformin does not work to lower glucose solely via hepatic mechanisms.

The diabetes phenotype is markedly different across ethnic groups; thus, it is likely that drug outcomes will differ between populations. The current and growing burden of diabetes is growing rapidly in all populations, particularly in South and East Asians, yet these populations are underrepresented in clinical and drug outcomes trials. A lack of systematic reviews and meta-analyses from these high-prevalence regions still points to differences in drug response. For example, the DPP4i response is greater in Asian than white people (108), a result supported by a subgroup analysis of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) showing a greater HbA_{1c} reduction to sitagliptin in East Asians compared with white individuals (109). Glycemic response to metformin has also been reported to differ by ethnic group, with African American individuals having a greater response than European Americans (110).

At this time, it is evident that we have the potential to use simple clinical (e.g., BMI, sex, ethnicity), physiological, and genetic variables to predict who is more or less likely to benefit from a treatment. The reducing costs of genotyping panels mean that genotype information could potentially be available at the point of prescribing, when the modest effect sizes described may start to have clinical utility. There is a need to develop implementation and evaluation strategies to assess the effectiveness and cost-effectiveness of such approaches compared with conventional treatment approaches.

PRECISION APPROACHES TO DIABETES IN PREGNANCY

In women, being affected by GDM is a major risk factor for T2D. The risk of developing T2D in women with prior GDM approaches 70% after the index pregnancy (111), climbing to an 84% risk of developing T2D in women of East Indian ancestry (112). Currently, genetic studies of GDM have identified those variants known to increase risk of T2D (113); however, other variants have been shown to influence glycemic traits specifically in pregnancy (114). Furthermore, like T2D, GDM is a heterogeneous condition linked to primary defects in either insulin secretion or sensitivity (115,116). GDM can also result from monogenic forms of diabetes, as numerous studies have shown. Models that attempt to predict pregnancy complications (117) or subsequent T2D (118) in GDM using clinical characteristics, biomarkers, and/or genetic variants have yet to be adopted, even though both lifestyle interventions and metformin use have demonstrated benefits in reducing the risk of T2D in women with prior GDM (119).

The target for all patients with T1D or T2D in pregnancy is to achieve as near normal glucose as possible, particularly around the time of conception (to reduce developmental anomalies) and in the third trimester (to reduce the risk of macrosomia) (120). In pregnancy, the only clear exception so far is for mothers with *GCK*-MODY (MODY2) as fetal growth is determined predominantly by fetal genotype (121). In mothers whose fetus inherits the mother's *GCK*-MODY mutation, fetal growth is normal despite the maternal hyperglycemia; thus, treatment of the maternal hyperglycemia is not recommended (121,122). Establishing whether the fetus is likely to be affected is usually determined by ultrasound scan. In the future, the use of noninvasive cell-free DNA methods in maternal blood will likely establish fetal risk (123). In GDM, whether maternal hyperglycemia is closely monitored and treated in the third trimester is based on the degree of hyperglycemia determined by an oral glucose tolerance test at 24–28 weeks' gestation (10). In the future, this decision could be modified by nonglycemic factors that impact fetal growth.

PATIENT-CENTERED MENTAL HEALTH AND QUALITY-OF-LIFE OUTCOMES

Precision diabetes medicine holds the promise of reducing uncertainty by providing therapies that are more effective, less burdensome, and with fewer adverse outcomes, which ultimately improve quality of life and reduce premature death (see Text Box 5). Highly relevant in this context is mental health (e.g., risk of distress and depression), yet little has been done to investigate how precision medicine might play a useful role in improving mental health outcomes.

Depression and anxiety are twice as common in people with diabetes than in the general population, occurring in up to 20% of adult patients (124). Distress occurs in ~30% of people with diabetes (125) reflecting the emotional and psychological burden that comes with diabetes and its complications, the life adjustments it requires, and anxiety about hypoglycemia or the impact on the fetus for GDM. Distress has been reported as being more common in patients in secondary rather than primary care and in populations with non-European ancestry. Depression is more common in lower- and middle-income countries, where ~75% of people with T2D reside (125). Both depression and distress in diabetes are more common in

those who progress from oral agents to insulin therapy (126). The onset of complications with the initiation of a more complex pattern of treatment is associated with increased rates of depression (126).

There are key points in the life course of a person with diabetes when both rational and irrational fears are often elevated, typically coinciding with "events," including:

- increased medication dose
- transition to insulin or other injectables or devices
- emergence of complications or worsening of complications
- following a severe hypoglycemic event
- change in diabetes care provider.

In many cases, patient self-evaluations may be distorted at these times because the patient attributes blame for the disease to themself, the future feels uncertain and distress peaks. In the setting of precision diabetes medicine, providers should assess symptoms of diabetes distress, depression, anxiety, disordered eating, and cognitive capacities using appropriate standardized and validated tools at the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance (127), information that, when combined with other data, are likely to improve the precision of clinical decision making.

Psychological counseling can help patients understand and manage their emotional reactions to major events by developing a more optimistic outlook and more realistic, modulated, and adaptive emotional reactions (128). Precision medicine may be used in the future to help predict the frequency and extent of emotional crises. As a result, precision diabetes medicine may lessen the patient burden, help patients to objectivize their disease, and provide targets for behavioral and point-of-care interventions at critical moments in the clinical care cycle. Effective and tailored education and professional counseling will be necessary to mitigate the risk that a clearer prognosis may raise anxiety about the future for some patients.

EQUITY IN PRECISION DIABETES MEDICINE

The experience with monogenic diabetes has shown that there is a large degree of regional, national, and international variation in how, and how often, these cases are diagnosed (1,129,130). This variation is, in part, due to differences in access to general medical care and treatments, access to relevant health care professionals with the necessary education, training, and experience, and access to laboratories with the necessary experience, assays, and standards (131). A precision approach to diabetes care will require that the relevant laboratory methods and assays are carefully standardized and comparable. Assessments that need to be standardized include:

- T1D-associated autoantibodies
- C-peptide
- clinical genetic/genomic risk scores
- decision-support interpretation.

A challenge is that the frequency of various diabetes phenotypes and risk genotypes may vary by regions of the world and between ethnicities within a region. For example, T2D often manifests very differently in Native Americans than in people of European ancestry, with Native Americans tending to develop diabetes at a much younger age and experience loss of β-cell function earlier in the life course of the disease (132). Recent insights following the ADA Precision Diabetes Medicine meeting in Madrid (held in October 2019) confirm that case-based interactive learning is an excellent way to support this type of postgraduate education for clinicians at all levels of training.

THE ROAD TO IMPLEMENTATION

Advances in science allow for generation of large-scale biological and physiological data that can be harnessed for precision diagnostic (Fig. 2), therapeutic (Fig. 3), and prognostic (Fig. 4) purposes. Programs are needed to train, foster, and retain individuals with biological and data science expertise who will contribute to precision diabetes medicine efforts. Furthermore, clinicians, scientists, and regulators must collaborate to develop standards and safeguards for protecting the accumulated "precise" data, which in some instances may lead to unintended and sensitive revelations, on individuals in a secure manner across populations and across countries. Worldwide differences in prevalence of the forms of diabetes necessitates inclusion of currently understudied populations for the development of precision diagnostics and therapeutics. As a result, the precise subtype of diabetes a particular individual is diagnosed with may vary in different populations based on subtype frequency or genetic or dietary or lifestyle differences.

The communication strategy used by the interventionalist and the patient's perception of risk may be important factors contributing to the successful implementation of precision diabetes medicine. Both personal and societal barriers may exist to the implementation of precision prevention across geographic regions and countries. Discussions with global and regional regulatory agencies will be needed to determine the level of evidence needed for approval and adoption of precision diagnostics and therapeutics. The development of tools and strategies to synthesize patient data and facilitate shared decision making will be needed to translate evidence for precision diabetes medicine into individualized diabetes care, accounting for patient preferences and behaviors, health literacy, and socioeconomic considerations. Pragmatic studies of decision-support systems utilizing rich information in these health care systems, particularly those with biobank-linked electronic health care records, are needed to guide implementation of precision diabetes medicine into clinical practice and to generate the much needed cost-efficacy data for broader adoption.

BUILDING PARTNERSHIPS

Partnerships must be established between the scientific community, patients, health care systems, providers, payors, industry, and regulatory bodies involved in the development, evaluation, approval, adoption, and implementation of precision diagnostics, monitoring, and therapeutics that are deemed acceptable for safe, efficacious, and cost-effective use in precision diabetes care. Making the most of the opportunities offered by precision diabetes medicine will require many different stakeholders to form highly effective partnerships. Without networks of partnerships that span academic institutions, corporations, payors, regulators, and medical and public interest groups with shared understanding and

vision (Fig. 5), precision diabetes medicine is destined to fail. Partners in making precision diabetes medicine a reality include:

People with diabetes. People with diabetes are the most important stakeholders. In Western countries, between 1 in 10 and 1 in 20 people have diabetes, while in other parts of the world, diabetes is more prevalent (1 in 3 in some Middle Eastern populations (133), and 1 in 2 in some Native American tribes [132]). The precision approach to diabetes will require effective patient-facing, bidirectional communication strategies that explain what precision medicine is and how it works. People with diabetes should be invited to contribute to research through advisory and advocacy positions, to contribute to postgraduate educational programs for clinicians and to play a central role in discussions with politicians, regulators, and payors.

Regulatory agencies. The transition from current diabetes clinical practice to a precision medicine approach will have important implications for the development, prescription, and regulation of diagnostics and therapeutics. Involvement of regulators at the earliest stages of the precision diabetes medicine workflow will be critical to the successful implementation of the precision approach. Recognizing these challenges, the FDA and the European Medicines Agency have initiated discussions relating to standards for evidence and the design of future clinical trials for precision diabetes medicine (134).

Payors. Payment for medical care related to diabetes varies greatly, including between regions within countries, with costs for diabetes often hidden in other areas of medical care. Fragmentation of sites of delivery for diabetes care and its costs directly impact payment policies. There is evidence in the case of monogenic diabetes that a precision medicine approach is cost-effective (135). The delay, or prevention, of complications (the major contributor to diabetes costs) through precision diabetes medicine may be the strongest driver for adoption.

Product manufacturers. Diabetes technology, including the development of wearable devices for glucose monitoring and for regulating insulin infusions (i.e., the artificial pancreas), has developed rapidly and is an example of widespread personalized diabetes medicine. Technology and pharmaceutical implementation is currently at a pre-precision level, and treatment guidelines are quite generic. The European Federation of Pharmaceutical Industries and Associations (EFPIA) Diabetes Platform, in which six leading pharmaceutical companies are developing shared policy goals focused on improving diabetes clinical outcomes, has initiated multiple projects with strong precision diabetes medicine agendas, with other public-private partnerships focused on precision diabetes medicine underway (136).

Private and public supporters of research. Support for diabetes research funding has struggled as its priority has fallen among the general public and some political decision makers, where cancer and cardiovascular disease rank consistently higher than diabetes on the public agenda. For precision diabetes medicine to meaningfully improve the lives of patients, it will be necessary to build highly effective networks of key stakeholders, such that common agendas are agreed to and funding for research and implementation is made available. This, in turn, requires that the evidence justifying a precision diabetes medicine approach is clearly articulated to all major decision makers, including funders.

Clinicians and professional organizations. Medical care for the person with diabetes involves a wide spectrum of health care providers, including tertiary and secondary specialists, general internists, primary care doctors, nurses, dietitians, podiatrists, pharmacists, and other paramedical professionals. Several organizations are engaged in the PMDI (ADA, EASD, NIDDK) and representatives of professional bodies in Asia, Africa, and elsewhere are being engaged by the PMDI to ensure global impact. Tailoring educational modules and content to different professional and cultural settings is ideally suited to these partner organizations.

General public. The enormous burden that diabetes places on many health care systems is usually shouldered by the general public, owing to the high costs of treating the disease and loss of public revenue through decreased productivity. The effective implementation of precision prevention will require that the general public embraces the approach and that those in greatest need can access precision prevention programs. Diabetes messaging for the general public can be modeled on precision oncology, for which public advocacy and engagement have been successful, effectively utilizing social media as well as traditional media to communicate not only its strengths and weaknesses but also its benefits and risks.

SUMMARY AND FUTURE PERSPECTIVES

Precision diabetes medicine has found a firm foothold in the diagnosis and treatment of monogenic diabetes, while the application of precision medicine to other types of diabetes is at this time aspirational, rather than standard of care. The ability to integrate the diagnosis of monogenic diabetes into routine clinical care is one example where diagnostics are essential and meet many of the characteristics of the ideal test. Despite an excellent diagnostic paradigm, there are no known avenues for prevention in monogenic diabetes, although careful monitoring in presymptomatic variant carriers may lead to early detection of diabetes and rapid treatment.

Future precision diabetes medicine approaches are likely to include diagnostic algorithms for defining diabetes subtypes in order to decide the best interventional and therapeutic approaches. The scope and potential for precision treatment in diabetes is vast, yet deep understanding is lacking. It will be imperative to determine when and how the application of therapeutics in precision diabetes medicine improves outcomes in a cost-effective fashion.

There are many important stakeholders whose engagement will be necessary for the implementation of precision diabetes medicine to succeed (Fig. 5). Progress in translating advances in biology and technology will be governed by the identification, accurate measurement, and scalable deployment of agents for diagnosis and therapy, so broad stakeholder engagement is essential. It is crucial that precision approaches are available to the full diversity of human populations and societal contexts, such that precision diabetes medicine does not widen health disparity but achieves

the greatest benefits to all individuals and society as a whole. Highly functional partnerships with patient representatives and public organizations will be required to reap the benefits of precision diabetes medicine.

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